CHAPTER

69 The Nephrotic Syndrome

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The nephrotic syndrome is defined by the triad of proteinuria (>3–3.5 g per day), hypoalbuminemia (<3 g per dL), and edema. Most patients also present with hypercholesterolemia. The nephrotic syndrome is the consequence of protein loss caused by severe injury to the glomerular capillary wall, and thus a typical presentation of patients with a glomerular disorder.[1] The nephrotic syndrome should be discerned from nephrotic range proteinuria. Patients with nephrotic range proteinuria have normal or only slightly decreased serum albumin levels, and are often asymptomatic. Nephrotic range proteinuria with preserved serum albumin levels is characteristic of focal segmental glomerulosclerosis (FSGS) related to hyperfiltration.[1,2]

Complications of the nephrotic syndrome mainly result from protein loss in the urine (Table 69.1). Edema formation is the best known presenting complication of the nephrotic syndrome. Patients with the nephrotic syndrome may also have hormonal disturbances, and are at increased risk for infections, venous thromboembolism, cardiovascular events, and acute renal failure. Finally, proteinuria is the best independent predictor of progression to chronic renal failure, and patients with persistent nephrotic syndrome will almost invariably develop end-stage renal disease (ESRD).

EDEMA

Edema in the nephrotic syndrome is typically seen around the eyes in the morning, and in the lower legs and feet in the evening. Edema can be massive, resulting in weight gain of >10 kg. Edema is the consequence of an alteration in the balance of forces that govern the fluid exchange over the capillary wall as reflected in the Starling equation: $Jv = LpS\{(P_{plasma}-P_{int}) - \sigma(\pi_{plasma}-\pi_{int})\}$, where transcapillary fluid flux (Jv) is determined by the hydraulic conductivity (Lp) and the filtration surface area (S) of the capillary wall, the differences between the hydrostatic (P) and oncotic (π) pressures in plasma and interstitium (Int), and the transcapillary reflection coefficient for proteins (σ).[3] In patients with the nephrotic syndrome the hypoalbuminemia and the subsequent decrease of plasma oncotic pressure increases net capillary ultrafiltration. Initially, accumulation of interstitial fluid (and thus edema) is partly prohibited by "edema prevention forces" such as an increase in interstitial hydrostatic pressure, and increased interstitial fluid transport and lymph drainage, which transfers interstitial proteins back to the vascular compartment resulting in a decrease in interstitial oncotic pressure and unchanged $\Delta\pi$.[4] Edema develops when these opposing forces are overwhelmed.

Obviously, edema formation requires ongoing renal sodium and water retention. Two theories have been proposed to explain the sodium retention in the nephrotic syndrome. These theories and the potential afferent and efferent mechanisms of sodium and water reabsorption in the nephrotic syndrome are illustrated in Figures 69.1 and 69.2. In the underfilling theory hypoalbuminemia and the ensuing hypotonicity causes fluid loss from the intravascular space. The resultant decrease of plasma and blood volume will activate homeostatic responses which drive renal sodium retention. The overfill theory of edema formation postulates that there is primary, abnormal renal sodium retention related to intrinsic abnormalities of the kidney. In this respect patients with the nephrotic syndrome differ from patients with edema formation due to heart failure and cirrhosis of the liver, in which the kidneys are structurally normal. Indeed, in comparative studies nephrotic patients were characterized by a relatively higher arterial blood pressure, a higher glomerular filtration rate (GFR), and less impairment in sodium and water excretion.[5]

In the following paragraphs we review the evidence to support these theories, discuss new pathogenetic mechanisms, and evaluate treatment modalities. We also address other complications of the nephrotic syndrome.

RENAL SODIUM AND WATER RETENTION IN THE NEPHROTIC SYNDROME: CLINICAL OBSERVATIONS

For a long time the theory of transcapillary fluid transport, governed by the principles of the Starling equation, dominated the discussion of edema formation in the nephrotic syndrome. A reduction in the amount of circulating albumin,

69.1 Complications of the Nephrotic Syndrome

Complication	Cause	Specific Treatment[a]
Edema	Loss of albumin	Sodium restriction Treatment with (combination of) diuretics
Hypothyroidism	Loss of thyroid hormones	Rarely supplementation with thyroid hormones necessary
Osteoporosis	Loss of vitamin D Binding protein	Treatment with vitamin D_2/D_3
Anemia	Loss of erythropoietin	No treatment Only in case of severe disabling anemia consider treatment with erythropoietin[b]
Infections	Loss of IgG	Antibiotic therapy In case of persistent nephrotic syndrome: Pneumococcal vaccination Prophylactic IgG may be useful in case of recurrent bacterial infections and hypogammaglobulinemia
Thrombosis	Loss of anticoagulant proteins	Consider prophylactic anticoagulation in patients with membranous nephropathy and serum albumin <2 g/dL or patients with serum albumin <2 g/dL and additional risk factor for thrombosis[c]
Cardiovascular events	Hyperlipidemia	Dietary restriction of cholesterol and saturated fat HMG CoA reductase inhibitors
Renal failure	Intrinsic renal injury Loss of transferrin with iron Proteinuria	Reduction of proteinuria and blood pressure with ACE inhibitor/ARB

[a]All patients should receive treatment aimed at the underlying disease and aimed at reduction of proteinuria preferably using ACE inhibitor/ARB.
[b]Other causes of anemia should be excluded first.
[c]Risk factors for thrombosis: previous thromboembolic event, prolonged bed rest or immobility, congestive heart failure.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IgG, immunoglobulin G; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

which is the major determinant of oncotic pressure, will promote transport of water across the capillary wall toward the interstitium. As a result plasma and blood volume will decrease. It was proposed that in patients with a nephrotic syndrome plasma and blood volume were (partly) maintained by sodium and water retention that increased the extracellular volume.[6] This increased sodium reabsorption was attributed to neurohumoral activation and renal hemodynamic changes as a consequence of the decreased blood and plasma volume.

Many studies have provided data that are in line with the sequence of events as depicted in Figure 69.1, and thus support the underfilling theory of sodium retention in the nephrotic syndrome. There is no doubt that plasma and blood volume can be severely compromised in children with a nephrotic syndrome. Van de Walle et al. reported in detail nine children with multirelapsing nephrotic syndrome due to minimal change disease.[7] These patients were studied during a severe relapse, with serum albumin concentration averaging 1.6 g per dL. The patients had symptoms of hypovolemia such as tachycardia, oliguria, peripheral vasoconstriction, and abdominal pain. These children had low GFR; elevated levels of renin, aldosterone, and vasopressin; and a markedly increased proximal tubular sodium reabsorption. Oliver studied seven children with steroid sensitive nephrotic syndrome, and observed increased urinary norepinephrine excretion in the nephrotic phase.[8] Urinary norepinephrine was positively correlated with plasma aldosterone and negatively with urinary sodium excretion. In studies that followed, these investigators showed that volume expansion with intravenous administration of albumin lowered plasma norepinephrine levels.[9] Gur et al. studied six children with lipoid nephrosis.[10] In the period of nephrosis these patients had reduced electrolyte-free water clearance, compatible with increased proximal tubular sodium reabsorption.

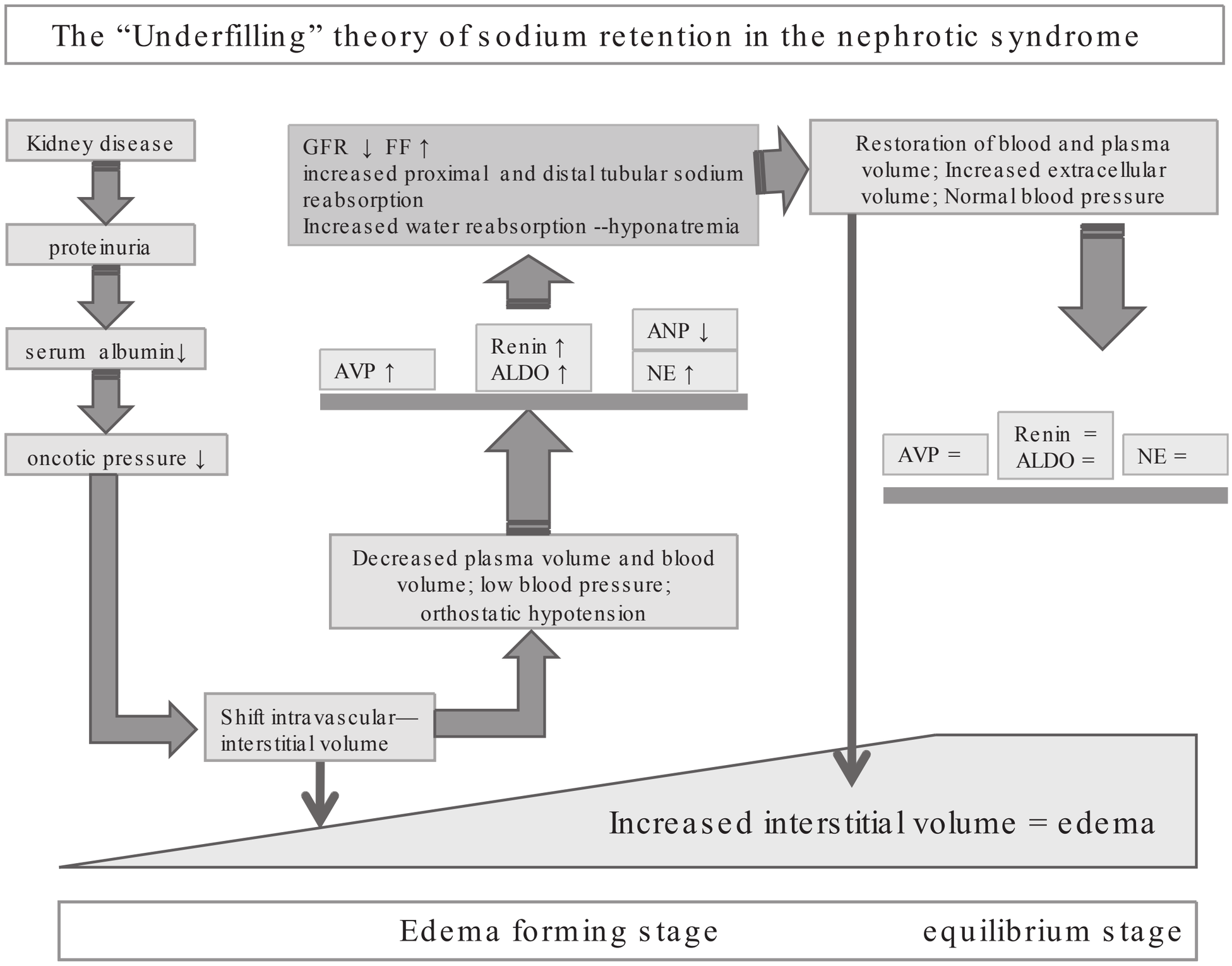

FIGURE 69.1 Pathophysiology of sodium retention in the nephrotic syndrome: the underfilling theory. Severe proteinuria and decreased serum albumin levels are the hallmark of the nephrotic syndrome. Capillary oncotic pressure decreases, resulting in increased capillary ultrafiltration. Edema will develop as soon as the edema preventing mechanisms are overwhelmed. In the edema forming phase, interstitial volume is increased and plasma volume is decreased. This will stimulate renal sodium and water reabsorption, true activation of neurohumoral mechanisms (catecholamines, renin, aldosterone, arginine vasopressin), changes in renal hemodynamics (low glomerular filtration rate, increased filtration fraction), and altered peritubular forces (increased oncotic pressure, decreased hydrostatic pressure). Ongoing water and sodium retention will normalize plasma and blood volume, at the cost of a large increase in extracellular volume, thus increasing edema. In the equilibrium phase, many parameters may be normalized. *ANP,* atrial natriuretic peptide; *AVP,* arginine vasopressin; *GFR,* glomerular filtration rate.

Support for underfilling is not limited to studies in children with steroid sensitive minimal change nephrotic syndrome. Yamauchi and Hopper described 10 adult patients who presented with hypotension and hypovolemic shock as complications of the nephrotic syndrome.[11] These patients had severe hypoalbuminemia, amounting 1.4 g per dL (range 0.4 to 2.2 g per dL). Blood volume was reduced to values ranging from 71% to 92% of the predicted values. Kunagai studied 11 patients with a nephrotic syndrome due to minimal change disease and relatively well preserved renal function.[12] These patients were studied in the stage of edema formation, during diuresis, and in remission. In the edema forming stage, the patients retained sodium and their body weight increased by >0.2 kg per day. Blood pressures were low to normal, ranging from 113/71 to 142/90 mm Hg. In the edema forming stage plasma volume (measured in supine position) was decreased, and plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were increased. PRA correlated with plasma volume and PAC, and sodium excretion was lowest in patients with highest PAC. Evidence to support the role of aldosterone in sodium retention comes from clinical studies, in which spironolactone, a selective mineralocorticoid receptor antagonist, was used. Shapiro et al. studied patients with a nephrotic syndrome and a high sodium intake. Within 3 days after the start of therapy sodium excretion increased from 205 ± 20 mmol per day to 312 ± 13 mmol per day in patients on spironolactone, and remained stable in controls.[13] Other investigators evaluated the role of arginine

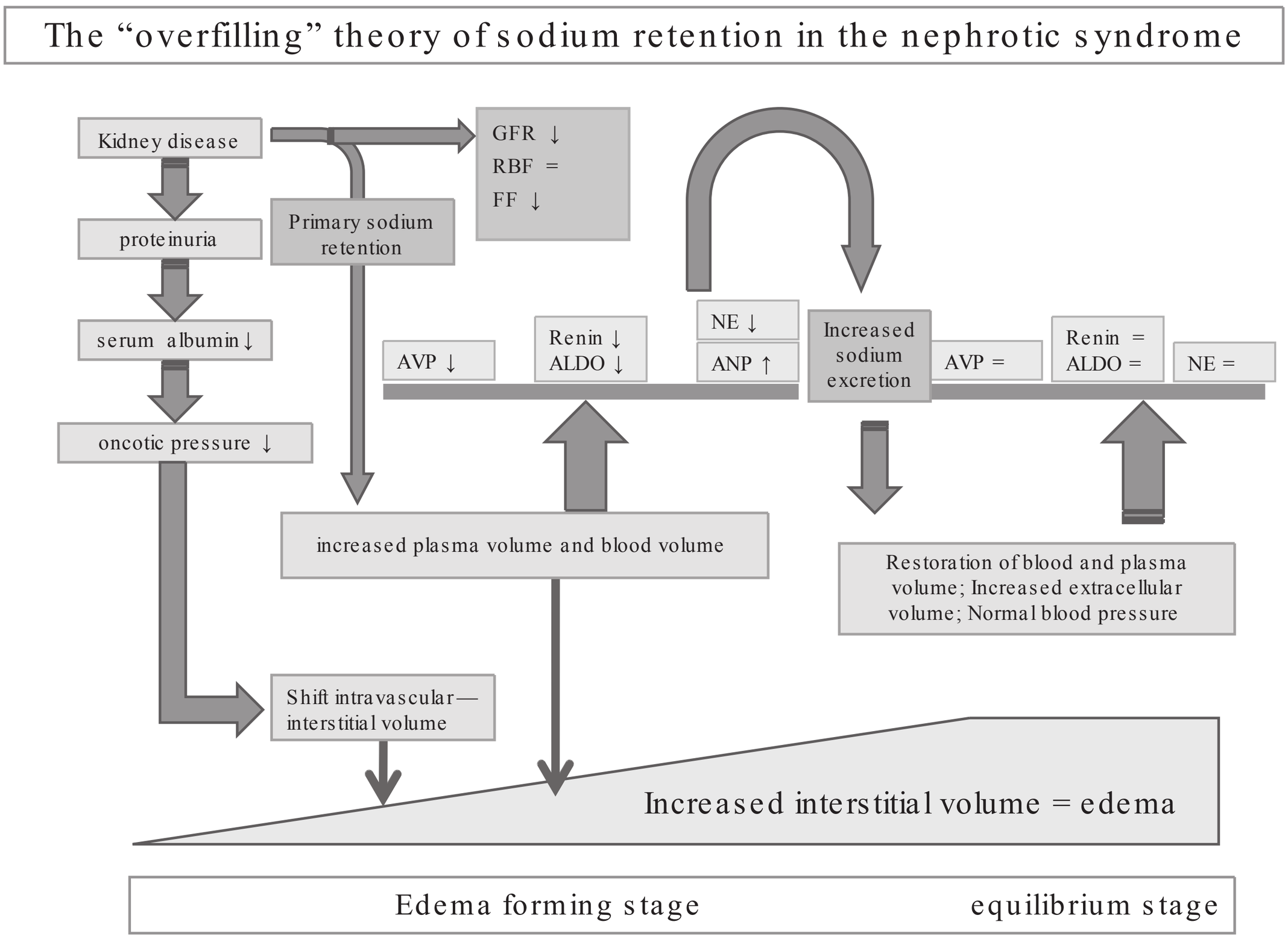

FIGURE 69.2 Pathophysiology of sodium retention in the nephrotic syndrome: the overfill theory. Kidney injury causes proteinuria and decreased serum albumin levels. Capillary oncotic pressure decreases, resulting in increased capillary ultrafiltration. Edema will develop as soon as the edema-preventing mechanisms are overwhelmed. Kidney injury also causes primary renal sodium retention. Possible mechanisms include increased activity of the epithelial sodium channel, decreased responsiveness to atrial natriuretic peptide (ANP), in addition to low glomerular filtration rate. Sodium and water retention will increase extracellular volume, with a disproportionate increase of interstitial versus plasma volume due to the altered capillary forces. Patients will present with normal or elevated plasma volume, blood pressure, and ANP, and decreased renin and aldosterone. Patients with overfilling will respond less well to volume loading, and efficacy of spironolactone may be impaired. Finally, sodium retention will cease, if equilibrium is reached. *ANP,* atrial natriuretic peptide; *AVP,* arginine vasopressin; *GFR,* glomerular filtration rate.

vasopressin (AVP). Usberti et al. studied 16 patients with a nephrotic syndrome, all with normal blood pressure and normal renal function.[14] These patients were studied while in equilibrium (no weight gain). For comparison, patients with glomerulonephritis were evaluated. The nephrotic patients had lower plasma sodium concentration and blood volume, and increased levels of plasma AVP, PRA, and urine epinephrine. Patients with the nephrotic syndrome were unable to excrete a water load: maximal urinary flow rate was 4.52 ± 1.71 mL per min (vs. 10.0 ± 2.26 mL per min in controls) and minimal urine osmolality 161 ± 50 mOsm per kg (vs. 83 ± 8 mOsm per kg). The conclusion that in the nephrotic syndrome AVP was non-osmotically stimulated was supported by subsequent experiments which showed that iso-osmotic volume expansion with human albumin decreased AVP, and increased water diuresis. Other maneuvers to increase plasma volume in patients with a nephrotic syndrome, such as water immersion and head down tilt, also increased diuresis and natriuresis.[15–17] The sympathetic nervous system has also been studied in adults with a nephrotic syndrome.[18] Sympathetic nervous system activity was assessed in six patients with a nephrotic syndrome and in six normal control subjects in the supine position. In the patients the plasma norepinephrine levels were elevated, the spillover rate of norepinephrine was markedly increased (0.30 ± 0.07 vs. 0.13 ± 0.02 μg/min/m^2, $P < .05$), whereas the norepinephrine clearance rate was comparable to that in the normal subjects (2.60 ± 0.29 vs. 2.26 ± 0.27 L per minute, not significant). Of note, PRA

and plasma aldosterone, AVP, and ANP concentrations were not different in the nephrotic syndrome patients compared with control subjects.

Observations in the seventh and eighth decade of the past century provided arguments against underfilling as the only cause of renal sodium retention in the nephrotic syndrome. Dorhout-Mees et al. initially studied a group of 10 adult patients with minimal change nephrotic syndrome on 13 occasions.[19] The patients were selected for the study because of increased blood volume and blood pressure. Each patient was studied prior to and following prednisone-induced remission. After remission, blood pressure fell in 12 cases, plasma volume fell in 10 cases, and PRA increased in eight cases. Clearly, these data are most compatible with primary overfilling in the nephrotic syndrome (Fig. 69.2). Data from studies that followed supported the concept of primary renal sodium retention in the nephrotic syndrome. Geers et al. evaluated plasma and blood volume in 88 patients with nephrotic syndrome.[20] Plasma volume was 62.8 ± 9.6 mL per kg lean body mass (LBM) in nephrotic patients and 56 ± 7.1 mL per kg LBM in controls, and blood volume was 94.9 ± 15.1 mL per kg LBM in nephrotic patients versus 88.5 mL per kg LBM in controls. Blood pressures in these and other patients with a nephrotic syndrome were normal or slightly increased.[21,22] Further evidence to support overfilling comes from studies showing low PRA and PAC in many patients with a nephrotic syndrome.[21,23,24] Moreover, neither lowering aldosterone with captopril, blocking aldosterone with spironolactone, nor antagonizing angiotensin II with the analogue saralasin induced natriuresis.[23,25,26] It was also questioned if the increased levels of PRA that were observed in some patients with a nephrotic syndrome contributed to sodium retention. Brown et al. evaluated eight patients with a nephrotic syndrome and elevated PRA and PAC.[27] These patients were studied during treatment with captopril, which lowered PAC, and during treatment with intravenous (IV) albumin which decreased both PRA and PAC. Both interventions failed to restore sodium balance. The blood pressure, however, fell with captopril and could have obscured a natriuresis secondary to a decreased PAC.

Additional renal hemodynamic studies and studies of tubular function also supported the overfilling theory. Geers et al. measured GFR using Cr^{51}–EDTA clearance and ERPF using J^{131}–hippurate clearance in 41 patients with a nephrotic syndrome.[21] Mean filtration fraction was low, and averaged 14%, arguing against underfilling and a stimulated renin-angiotensin-aldosterone system (RAAS). Detailed clearance studies showed that proximal tubular sodium reabsorption was decreased rather than increased. Usberti et al. studied 21 patients with glomerulonephritis.[28] Tubular glucose reabsorption was used as a marker of proximal tubular sodium reabsorption. The threshold for glucose reabsorption was reduced in the 10 nephrotic patients with edema, suggesting diminished proximal tubular reabsorption. In studies undertaken in five nephrotic patients, a similar conclusion was reached by Grausz et al.[29] In these clearance studies, blockade of sodium reabsorption in the distal nephron with ethacrynic acid and chlorothiazide was used to assess proximal sodium reabsorption. Proximal sodium reabsorption was lower in the nephrotic patients than in normal and in cirrhotic patients.

Studies by Brown et al. and Koomans et al. also provided strong arguments against a role for hypoalbuminemia in the sodium retention of the nephrotic syndrome.[30,31] These investigators performed detailed clinical observations in patients who were treated with prednisone and developed a remission. In both studies there was a decrease of proteinuria after the start of prednisone. Immediately thereafter sodium excretion increased, well before any noticeable increase of serum albumin levels.

We must be cautious when interpreting the results of the various studies. It is important to consider the timing of the study, the characteristics of the study population, and study methodology. Studies may be done in the edema forming phase, or in the maintenance phase when patients are in equilibrium and many parameters may have normalized (Fig. 69.1). Patient characteristics include the underlying glomerular disease, the severity of renal injury, the level of GFR, and the rapidity of onset of the nephrotic syndrome. Methodology concerns include the methods used to assess plasma volume and blood volume, and the position of the patient. Measurements of plasma volume and blood volume are imprecise (coefficient of variance 10%). Studies have used different correction factors for plasma and blood volume, using body weight, dry weight, and estimated lean body mass. Plasma volume usually is calculated from the distribution of radioactive labeled albumin. Because the transcapillary escape rate of albumin is increased in patients with a nephrotic syndrome, blood samples must be taken shortly after administration of albumin. Blood volume is calculated from plasma volume or measured red cell mass and hematocrit. However, it is important to note that the ratio of peripheral hematocrit/whole body hematocrit (the so called F cell ratio) is lower in patients with a nephrotic syndrome. If this is not accounted for, calculated blood volume will be overestimated.

Another important issue is the role of body position. Most investigators have performed studies with patients in supine position. However, in patients with a nephrotic syndrome larger changes of plasma volume and blood volume occur upon change of body position. In 1960, Fawcett already studied patients with hypoalbuminemia and edema.[32] In these patients plasma and blood volume decreased to a larger extent compared to control patients as calculated from the change in hematocrit: after 60 minutes of standing hematocrit increased by 12.3 ± 3.4% in patients, and +6.6 ± 2.9% in controls. Similar findings were reported by Eisenberg and Geers.[33,34] Studies have shown that these changes are relevant, and affect natriuresis. Minutolo studied seven patients with a nephrotic syndrome and evaluated their baseline sodium excretion and the response to IV furosemide while supine and in upright position.[35] In the upright position patients had markedly higher levels of PRA and PAC, and lower sodium and water excretion. Similarly, the response to furosemide was attenuated in the upright position; 6-hour sodium excretion was 40.2 ±

7.8 mmol in the upright position and 64.1 ± 9.1 mmol while supine. Usberti also noted that fractional excretion of sodium was higher when patients were recumbent.[36]

Finally, interpretation of changes in levels of mediators of neurohumoral activation and effects of any intervention must be done with caution. Activation of PRA and sympathetic nervous system may occur as a consequence of the primary renal disease, and does not necessarily reflect underfilling. In contrast, effects of blockade of aldosterone may be masked by opposite effects of changes in blood pressure.

If we critically review the available literature, it is evident that patients with a nephrotic syndrome may present with characteristics of underfilling or overfilling. In the previously mentioned study of Van de Walle et al. only nine patients had clear signs and symptoms of hypovolemia. Ten other patients had no evidence of hypovolemia. When comparing children with and without hypovolemia, they observed higher PRA and PAC and lower blood volume in hypovolemic patients. These variations in volume status were also seen in children with a nephrotic syndrome caused by renal pathologies other than minimal change disease.[7] Similar observations have been done in adults (Table 69.2). Usberti et al. described two groups of nephrotic syndrome patients distinguished on the basis of their plasma albumin concentrations.[36] Patients in group 1 had a plasma albumin concentration of less than 1.7 g per dL associated with low blood volumes and atrial natriuretic plasma (ANP) levels, elevated plasma angiotensin II (AT-II) concentrations, and increased proximal tubular reabsorption of sodium (determined by lithium clearance). In contrast, group 2 patients with a plasma albumin concentration greater than 1.7 g per dL exhibited normal blood volumes and plasma hormone concentrations. In all patients blood volume was positively correlated with the plasma albumin concentration, and PRA was inversely correlated with both blood volume and plasma albumin concentration. Of note, GFR was not different between group 1 and group 2 patients (100 ± 25 vs. 101 ± 22 mL per minute, not significant), whereas urinary sodium excretion was substantially lower in group 1 patients (4.88 ± 5.53 vs. 29.9 ± 9.3 mEq per 4 hours, $P < .001$). Moreover, acute expansion of blood volume in group 1 patients normalized PRA, plasma AT-II and aldosterone concentrations, fractional sodium excretion, and lithium clearance, while increasing circulating ANP concentrations. Other studies have confirmed these findings, and have added relevant information. Meltzer et al. found that their hypervolemic patients tended to have more severe glomerular involvement, lower GFR, and hypertension.[37] In the study of Geers et al. this variability is also seen.[21] Patients were studied while in sodium balance, and studies were done with patients being recumbent. Overall, plasma volume, blood volume, and blood pressure were normal or above the normal range. There was a striking absence of a correlation between PRA

69.2 Clinical Characteristics of Patients with a Nephrotic Syndrome

	Patients with Sodium Retention	Patients in Sodium Balance
Number	12	8
Age	NA	NA
Gender	NA	NA
Blood pressure (mm Hg)	NA	NA
FENa (%)	0.107 ± 0.109	0.60 ± 0.170
GFR (mL/min)	100 ± 25	101 ± 22
S albumin (g/dL)	1.4 ± 0.28	2.2 ± 0.47
Proteinuria (g/day)	9.7 (5.7–22)	6.6 (3.2–10.2)
Blood volume (mL/kg)	68 ± 6	77 ± 4
Plasma renin activity (ng/mL/hr)	5.8 ± 3.5	0.61 ± 0.43
Plasma aldosterone (pg/mL)	337 ± 228	41 ± 20

NA, not available; GFR, glomerular filtration rate; FENa, fractional excretion of sodium; data are given as means (SD) or median (range).
Adapted from Usberti M, Gazzotti RM, Poiesi C, et al. Considerations on the sodium retention in nephrotic syndrome. Am J Nephrol. 1995;15:38–47.

69.3 Factors That May Give Guidance as to Whether an Individual Patient with the Nephrotic Syndrome Has Overfill or Underfill Edema

	Overfill	Underfill
GFR <50% of normal	+	−
GFR >75% of normal	−	+
Serum albumin >2 g/dL	+	−
Serum albumin <2 g/dL	−	+
Histology minimal change	−	+
Hypertension	+	−
Postural hypotension	−	+

GFR, glomerular filtration rate.
Reprinted from Schrier RW, Fassett RG. A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome. Kidney Int 1998;53:1111, with permission.

and blood volume. However, when critically analyzing the data, it is apparent that patients with minimal change disease had lower PV, and higher PRA and PAC. Within the group of patients with minimal change disease, renal impairment was associated with higher blood pressure, PV and blood volume, and lower PRA and PAC.

Thus, patients with nephrotic syndrome can show evidence of underfilling or overfilling. The effective plasma and blood volume in a particular patient will depend on the balance between the (rapidity) of the onset of the nephrotic syndrome, the severity of hypoalbuminemia, and the magnitude of primary renal sodium retention. Thus, underfilling may be more likely in patients with minimal change disease, preserved GFR, and severe hypoalbuminemia (Table 69.3).[37,38]

With respect to the mechanisms of primary renal sodium retention, these have remained largely undisclosed in human studies. The clearance studies have pointed to an intrarenal defect at the level of the distal tubules. Koomans et al. infused albumin in patients with nephrotic syndrome.[39] Patients had increased proximal and distal sodium reabsorption. Infusion of albumin decreased proximal but not distal sodium reabsorption, compatible with a hypovolemia dependent effect on proximal and a primary renal defect of distal sodium reabsorption. In humans, resistance to ANP has been suggested as the culprit. Jespersen studied seven patients with a nephrotic syndrome and 13 age- and sex-matched controls.[40] At baseline, patients had higher blood pressures, lower levels of plasma aldosterone, and higher levels of plasma ANP levels. Both patients and controls received a bolus of 2 ug per kg ANP. Although plasma levels of ANP reached similar levels, sodium excretion was significantly lower in patients. Most importantly, these authors observed that urinary excretion of the second messenger cGMP remained lower in the patients, suggesting a defective ANP signaling. Similar studies were done by Plum et al.[22] These authors studied 31 patients and 10 controls. ANP was infused over 2 hours in 15 patients and 10 controls. At baseline ANP levels were higher in the nephrotic patients. Infusion of ANP increased absolute sodium excretion to a similar extent, in patients and controls. However, sodium excretion factored for the level of ANP was reduced in patients. Again, urinary excretion of cGMP was lower in the patients. Fractional excretion of cGMP was calculated and used as marker of tubular production of cGMP. In the controls fractional excretion of cGMP increased from 93 ± 33% to 159 ± 142%, and in the patients fractional excretion decreased (from 166 ± 77% to 130 ± 58%.), indicating that indeed the tubular production of cGMP was attenuated in the nephrotic syndrome.

RENAL SODIUM AND WATER RETENTION: ANIMAL STUDIES

Earlier work in animal models strongly suggested a pathogenetic role for aldosterone and increased sympathetic activity in the nephrotic edema: adrenalectomy prevented the sodium retention in aminonucleoside nephrosis and renal denervation restored renal excretory function in the Adriamycin model.[41–43] Micropuncture studies in the rat nephrotoxic serum nephritis model found decreased single nephron GFR and increased proximal tubular sodium reabsorption.[44] Clearly, these findings support the underfilling theory (Fig. 69.1). However, these studies and their conclusions can be questioned. Sodium retention was not overcome by saline loading,[41] sympathetic activation may be the consequence of renal injury per se and is not necessarily proof of underfilling, and in the study of Kuroda proximal tubular pressures were increased suggesting distal tubular obstruction due to protein casts.[41,44]

Different conclusions were drawn in studies that followed. Many studies have used the "puromycin aminonucleoside (PAN)" model in the rat, which is considered a model of minimal change disease. Proteinuria is induced by intravenous injection of PAN. The animals develop proteinuria and hypoalbuminemia, often associated with edema and ascites. In the PAN model a short lasting increased sodium excretion is seen at day 1, followed by sodium retention from day 2 onward. Sodium retention preceded the onset of proteinuria which occurred after day 4.[45] This time course led investigators to conclude that sodium retention could not be the consequence of the proteinuria and the ensuing hypoalbuminemia. Although plasma aldosterone levels are increased at day 6 in this model, the role of aldosterone was questioned by experiments in adrenalectomized rats that received a constant supplementation with corticosteroids. In these "corticosteroid clamped" animals injection of PAN also

induced sodium retention.[46] Amiloride, but not the aldosterone receptor blocker sodium canrenoate, prevented sodium retention, thus confirming the limited role of aldosterone.[47] Additional studies indicated that sodium retention in this model was independent of systemic factors such as AVP, angiotensin II, PPARγ, nitric oxide, tumor necrosis factor alpha (TNFα), or insulin-like growth factor 1 (IGF1).[48] Deschenes and colleagues studied the activity and expression of the sodium transporters' epithelial sodium channel (ENaC) and Na-K-ATPase in the PAN model and two other models. In all models they observed an increased expression of these sodium transporters at the mRNA and protein levels in the collecting ducts. Activity of the Na-K-ATPase measured with a radioactive P^{32} labelled substrate was likewise increased and correlated with sodium excretion.[45] In similar experiments activity and expression of ENaC was increased.[46] Somewhat unexpectedly, adrenalectomy prevented the increase in expression of ENaC but not of Na-K-ATPase. Although these experiments indicate that sodium retention does occur in the absence of increased aldosterone levels, it cannot be ruled out that aldosterone plays a modulatory role. Recent studies evaluated sodium retention in mice that lacked the serum- and glucocorticoid kinase 1 (SGK1),which is induced by aldosterone and activates ENaC.[49] The nephrotic syndrome was induced by injecting doxorubicin. Sodium retention was less in the SGK1 knockout mice.

Bernard et al. performed experiments in a rat model of membranous nephropathy.[50] Micropuncture studies were done after volume expansion to limit the role of volume depletion. Urinary sodium excretion was decreased in the proteinuric rats. However, proximal tubular sodium reabsorption was not increased but decreased, and there were no differences in sodium load to the late distal tubules, suggesting that increased sodium reabsorption must have occurred beyond the late distal tubule. These findings were confirmed and extended in studies by Ichikawa et al. that virtually proved the existence of a renal defect beyond the late distal tubule as cause of the increased sodium retention in the nephrotic syndrome.[51] Ichikawa et al. selectively infused PAN in one kidney of Munich Wistar rats. They evaluated renal function, proteinuria, and single nephron function of both kidneys, which thus were exposed to the same systemic factors. Blood pressures were normal, as were serum protein levels. The data are depicted in Table 69.4. The diseased kidney was proteinuric, had slightly decreased GFR, and markedly decreased sodium excretion. Single nephron GFR and filtration fraction were decreased due to a reduction of the ultrafiltration coefficient Kf. Subsequent segmental analysis of sodium transport by micropunture showed that the amount of sodium that reached the end distal tubule was similar and amounted 0.31 nEq per minute in the perfused kidney and 0.32 nEq per minute in the nonperfused kidney. In the final urine sodium excretion was 0.08 nEq per min versus 0.24 nEq/min, indicating increased sodium reabsorption in the cortical or medullary collecting duct. Infusion of the angiotensin II blocker saralasin increased GFR but not sodium excretion, arguing against a role for the reduced GFR in the abnormal sodium excretion.[51]

69.4 Renal Parameters in the Unilateral Puromycin Aminonucleoside Model

	Perfused Kidney	Control Kidney
Systolic blood pressure (mm Hg)	118	118
Protein concentration (g/dL)	5.7	5.7
Proteinuria (mg/24 hr)	101	3
GFR (mL/min)	0.82	1.35
Urinary sodium excretion (μM/24 hr)	23	76
snGFR (nL/min)	31.8	48.6
snFF	0.25	0.35
ΔP (mm Hg)	35.4	35.5
Kf (nL/s.mm Hg)	0.047	1.02
Sodium delivery at site:		
Early proximal tubule (nEq/min)	5.6	8.2
Late proximal tubule (nEq/min)	3.3	4.4
Loop of Henle (nEq/min)	0.78	0.74
Late distal tubule (nEq/min)	0.31	0.32
Urine (nEq/min)	0.08	0.24

GFR, glomerular filtration rate; snGFR, single nephron GFR; snFF, single nephron filtration fraction; ΔP: glomerular transcapillary pressure gradient; Kf, glomerular capillary ultrafiltration coefficient

Adapted from Ichikawa I, Rennke HG, Hoyer JR, et al. Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. J Clin Invest. 1983;71: 91–103.

Although the above animal studies provided direct evidence for the existence of a primary renal tubular defect as cause of the impaired sodium excretion in the nephrotic syndrome, only recently have studies clarified the mechanisms involved in this defect.

Kastner studied the relationship between proteinuria and the expression of various ion channels in a mouse model of anti-GBM glomerulonephritis.[52] To dissociate the role of glomerular protein losses from tubular dysfunction studies were done in mice that partially lacked proximal tubule megalin

expression. In the diseased mice, expression of NHE3 and Na-Pi2b was decreased after injection of the antibodies, with no difference between the wild type and megalin knockout mice. Megalin knockout mice, in which reabsorption of proteins is markedly reduced, showed increased expression of fragments of αENaC and γENaC in the cortical region. In mice injected with the anti-GBM serum a further, substantial increase in the abundance of these fragments was seen, most prominent in the knockout mice. These findings were confirmed by immunohistochemistry. Similar observations by the same group were done in the rat anti-Thy-1.1 model.[53] Injection of anti-Thy1.1 antibody increased proteinuria, decreased GFR, and reduced sodium excretion. There was a major upregulation of bands of αENaC, γENAC, and Na-K-ATPase, and no change in the expression of NCC, NKCC2, and AQP2. These findings were considered compatible with increased proteolytic cleavage and thus activation of ENaC, related to the proteolytic activity of proteins in the urine. The direct role of proteinuria on renal sodium handing was substantiated in additional experiments. Svenningsen demonstrated that the nephrotic urine of patients and animals increased activity of ENaC in a cell line.[54] This effect was dependent on the presence in the urine of the serine protease plasmin. In patients with proteinuria, plasminogen is lost in the urine. Plasmin is generated by degradation of plasminogen under the influence of urokinase type plasminogen activator (uPA), which is present in the collecting ducts. In subsequent experiments it was shown that plasmin activates ENaC by cleaving and degrading an inhibitory peptide from the gamma subunit of ENaC.[55] These findings explain the efficacy of amiloride in this model; amiloride not only blocks ENaC, but also inhibits uPA.

Another potential mechanism of impaired renal sodium excretion involves ANP resistance. Perico et al. observed a blunted response to ANP in Adriamycin nephrotic rats.[56] This abnormal response preceded the water and sodium retention.[57] Valentin showed a blunted natriuretic response to infusion of saline in rats with Adriamycin nephrosis. Plasma ANP levels were higher in nephrotic rats.[58] Despite this, nephrotic rats excreted less cGMP, which was normalized by infusion of phosphodiesterase (PDE) inhibitors. There was no difference in ANP binding. These data suggested that ANP resistance was related to increased PDE activity. Similar findings were done in a Heymann nephritis model. Lower urine cGMP levels coincided with ANP resistance which was recovered by blocking PDE. Thus, these studies suggested that ANP resistance was caused by increased PDE activity.[59] Although resistance to ANP may be the consequence of volume depletion or concomitant neurohumoral activation, this is unlikely since volume loading did not alter the response to ANP, neither did renal denervation in some but not all studies. The absence of response to ANP in the isolated perfused kidney confirmed the renal defect.

A recent study pursued the potential mechanisms of ANP nonresponsiveness. Polzin studied rats made nephrotic by injection of PAN or anti-Thy-1 antibodies.[60] They observed a decreased expression of Corin in the medulla. Corin is a type 3 transmembrane serine protease that converts pro-ANP to the active ANP. Reduced Corin expression was paralleled by an increase in pro-ANP, decrease of ANP and cGMP, and an increased expression of beta-ENaC.

Although the animal studies provide convincing evidence for an intrarenal defect as cause of the altered sodium handling in the nephrotic syndrome, and the possible pathogenetic pathways are clarified in elegant in vivo and in vitro studies, a cautious note should be made: most animal models have used Adriamycin or puromycin aminonucleoside. These toxic agents not only cause glomerular injury, but may also cause direct tubular injury. As such, extrapolation of the findings in animal studies to the human situation should be done with caution. As reviewed above, the clinical observations clearly indicate that patients with the nephrotic syndrome can present with signs, symptoms, and laboratory findings of both underfilling and overfilling.

THERAPY OF SODIUM AND WATER RETENTION IN THE NEPHROTIC SYNDROME

The treatment modalities in nephrotic patients have been reviewed.[1] The first principle of treatment is to consider disease-specific treatment directed at the primary disease process, as reviewed in other chapters of this textbook. Non-disease-specific treatment is aimed at reducing proteinuria, retarding progression of renal failure, and preventing complications of the nephrotic syndrome.

Because edema formation is the consequence of renal sodium retention, restriction of dietary salt intake should be recommended to all patients. A sodium intake of between 2 and 3 g (87 and 130 mmol) per day is generally a reasonable compromise between effectiveness and palatability. However, if tolerated sodium intake can be further restricted to 1.2 g (50 mmol) per day, especially in patients with severe edema.[61] Water restriction is only needed if the patient is hyponatremic with hypo-osmolality. This is observed infrequently in patients with a nephrotic syndrome, and mostly related to too intensive diuretic therapy. Diuretic agents are needed if edema persists despite salt restriction.

In the treatment of edema of the nephrotic syndrome loop diuretics such as furosemide and bumetanide are often preferred since quantitatively most sodium is reabsorbed in the thick ascending limb of the loop of Henle.[62,63] Few controlled studies have compared the efficacy of loop diuretics in the nephrotic syndrome. Lau demonstrated that bumetanide in a dose of 2 mg was more effective than 80 mg of furosemide.[63] This was attributed to a greater effect of bumetanide on proximal tubular sodium reabsorption. Although furosemide and bumetanide are effective in the nephrotic syndrome, resistance to loop diuretics often occurs.

Diuretic resistance has been attributed to several factors, including variable gastrointestinal absorption (bioavailability),

impaired renal delivery, and tubular resistance. In normal subjects bioavailability of furosemide is quite variable and ranges from 10% to 100%.[64] The effect of the nephrotic syndrome on gastrointestinal absorption is debated. Prandota reported that absorption of an oral dose of 2 mg per kg of furosemide was significantly higher in nephrotic children than in control patients with urinary tract infection and mild hypertension.[65] Bioavailability in the nephrotic children averaged 58%. In another study in children, Engle demonstrated that an intravenous dose of 1 mg per kg furosemide was twice as effective as an oral dose of 2 mg per kg.[62] Thus, a low bioavailability could explain apparent resistance to seemingly adequate doses of furosemide. This can be overcome by increasing the oral dose, administering oral bumetanide or torsemide which are absorbed more predictably (80%–100%), or by intravenous administration of the diuretic.[64]

Loop diuretics are highly bound to albumin and it has been postulated that hypoalbuminemia may result in an impaired delivery of diuretics to the kidney and reduced tubular secretion. In analbuminemic rats there indeed is insufficient delivery of loop diuretics into the tubular fluid.[66] Data from more recent studies challenge the importance of hypoalbuminemia as a cause of decreased delivery of furosemide. Fliser et al. found no significant difference in urinary furosemide excretion in patients with nephrotic syndrome (mean serum albumin 3.0 g per dL) after 60 mg furosemide IV (34.9 ± 3.7 mg) compared to furosemide 60 mg plus 40 g human albumin IV (35.1 ± 4.2 mg).[67] Moreover, only a modest increase in sodium excretion was observed after furosemide plus human albumin (312 ± 28 mmol) compared to furosemide alone (259 ± 30 mmol). The increased natriuretic action appeared to be mainly mediated by changes in renal hemodynamics but not increased delivery of furosemide. Similarly, Agarwal et al. showed that ample furosemide reached the urine in patients with nephrotic syndrome.[68]

Akcicek et al. administered a maximal dose of furosemide (bolus of 60 mg followed by 40 mg per h) to eight severely nephrotic patients (serum albumin 1.1–2.2 g per dL).[69] Neither sodium excretion (934 ± 355 μmol per min) nor volume of urine (8.49 ± 2.9 mL per min) increased with coadministration of 0.5 g per kg albumin (respectively 884 ± 453 μmol per min and 9.21 ± 4.11 mL per min).

Davison et al. treated 12 nephrotic patients, referred for a diuretic-resistant state, with furosemide in increasing doses to 500 mg per day.[70] Spironolactone up to 200 mg per day was added if diuresis did not occur with furosemide. Nine of 12 patients had a creatinine clearance rate of less than 40 mL per minute. Six (50%) patients (median serum albumin 2.2 g per dL; range 1.3–2.3 g per dL) responded satisfactorily to increased diuretic therapy. However, in the remaining six patients (median serum albumin 1.7 g per dL; range 0.9–1.8 g per dL), diuresis either was unsuccessful (two patients) or resulted in serious complications, including increasing blood urea nitrogen in three patients and hyponatremia in one patient. In the six unresponsive patients, 300 mL of a 15% solution of salt-poor albumin led to a significant diuresis and resolution of edema without worsening renal function. Thus, furosemide with albumin may be especially useful in patients with minimal change disease and severe hypoalbuminemia (<2.0 g per dL) who appear volume depleted.[71,72]

Both studies in animals and humans have shown that there is tubular resistance to the effects of loop diuretics in nephrotic syndrome.[73] Nephrotic patients show a lesser natriuretic response to equivalent excretion rates of furosemide compared to normal controls.[74,75] The resistance to furosemide has initially been attributed to its binding to albumin within the tubular fluid rendering the diuretic inactive.[76] However, blocking of albumin binding to furosemide by the administration of sulfisoxazole had no effect on diuretic reponse.[68] Although definitive conclusions cannot be drawn since patients included in the study were not diuretic resistant, the results suggest that decreased tubular responsiveness to loop diuretics and/or increased sodium reabsorption at other tubular segments are more important causes of diuretic resistance. In PAN nephrotic rats loop chloride reabsorption as a percentage of delivered load was inhibited to a lesser extent (67.9 ± 4.7%) by IV furosemide compared to normal rats (48.3 ± 3.0%), suggesting that the loop of Henle may be relatively resistant to loop diuretics.[73] Alternatively, furosemide resistance might be due mainly to the increased potency of the cortical collecting duct to reabsorb an overload of sodium. A recent study by Deschenes et al. showed normal intrinsic sensitivity of the loop of Henle in PAN nephrotic rats.[47] In contrast, in vitro perfused CCD isolated from sodium-retaining PAN nephrotic rats exhibited an extremely high transepithelial sodium reabsorption.

In view of the experimental data demonstrating enhanced sodium reabsorption in the collecting tubules, potassium-sparing diuretics that act at this level (e.g., amiloride) would also be expected to be efficacious in treating nephrotic edema. Indeed in PAN nephrotic rats administration of amiloride increased sodium excretion, normalized sodium balance, and reduced ascitic volume.[54] Preliminary data from Deschenes et al. suggest that in nephrotic patients amiloride may have similar natriuretic effects as furosemide. In six nephrotic children treatment with amiloride resulted in a negative sodium balance of −33.8 ± 48.3 mmol/m^2/day.[47] The sodium balance was comparable to a group of seven nephrotic children treated with furosemide alone (−23.4 ± 29.9 mmol/m^2/day).[77]

The response to mineralocorticoid antagonists such as spironolactone varies. Spironolactone can induce a mild but significant natriuresis in nephrotic patients with an activated RAAS,[13,23] whereas its effect is absent in nephrotic patients with a normal plasma aldosterone.[23] Currently these data are not sufficient to advise monotherapy with amiloride or spironolactone.

Based on the pathophysiologic concepts, it seems plausible that in patients with severe nephrotic syndrome who do not respond satisfactorily to treatment with a loop diuretic addition of amiloride, spironolactone or a thiazide diuretic may be considered.[70,78] Based on experimental data amiloride would be the first choice if serum potassium is

normal. Deschenes administered furosemide and amiloride to seven nephrotic children which resulted in a negative sodium balance of −73.8± 55.4 mmol/m^2/day compared to −23.4± 29.9 mmol/m^2/day (P < .05) in controls using only furosemide.[77] Further evidence is certainly needed.

In daily practice, diuretic therapy for nephrotic syndrome often can be instituted in the outpatient setting.[1] Patients should be instructed to weigh themselves daily and to diminish or discontinue the diuretic if weight loss exceeds 0.5 kg per day or when edema no longer becomes a source of discomfort. Patients should also reduce or discontinue the diuretic when orthostatic lightheadedness develops. An oral thiazide diuretic is a reasonable first choice in patients with mild edema and a normal GFR (>50 mL per min).[79] Loop diuretics are indicated in case of more severe edema or renal insufficiency. Because of the previously described resistance to loop diuretic action often higher doses are required to achieve effective renal sodium excretion. The absence of a significant diuresis following ingestion of a loop diuretic usually is an indication of low tubular diuretic concentrations. Increasing the dose is indicated. Loop diuretics have a rather short half-life, and the initial natriuresis may be counterbalanced by avid sodium retention during the rest of the day. Therefore, if weight loss is insufficient in patients who respond with initially appropriate diuresis, dosing twice daily will be more effective. The total daily dose may be as high as 500 to 1,000 mg for furosemide. If natriuretic response is insufficient, amiloride, spironolactone, or a thiazide can be added. It is important to realize that the simultaneous use of diuretics from different classes increases the risk of volume contraction and potassium disturbances. Patients who do not respond to oral treatment can benefit from intravenous administration of loop diuretics. Only if these regimens fail a trial of albumin and furosemide may be indicated, especially in patients with minimal change disease and severe hypoalbuminemia (<2.0 g per dL) who appear volume depleted.[71,72] However, this form of therapy remains relatively expensive, and the diuretic effects of albumin infusion are usually short-lived.[39] Hospitalization may be required to initiate and monitor diuresis especially in the latter patients with either severe edema or marked hypoalbuminemia, especially when a significant decrease in GFR is present.

OTHER COMPLICATIONS OF THE NEPHROTIC SYNDROME

In patients with a nephrotic syndrome urinary losses of albumin are not fully compensated by the increased hepatic production, with hypoalbuminemia and edema as a consequence.[80] Many other proteins beside albumin are lost in the urine in the nephrotic syndrome. Among these are hormones and hormone-binding proteins, immunoglobulins, and proteins involved in the coagulant system. As a consequence patients with a nephrotic syndrome may present with anemia, infections, thrombosis, hypothyroidism, and vitamin D deficiency (see Table 69.1). In addition, patients with a nephrotic syndrome are at increased risk of atherosclerotic vascular disease and progression to ESRD.

Hormonal Disturbances

Many hormones are large proteins or protein bound molecules, and increased losses may occur in patients with a nephrotic syndrome. Loss of albumin and thyroid-binding globulin may reduce the binding capacity for thyroid hormones, resulting in a decrease in total triiodothyronine (T3) and thyroxin (T4) concentrations. Furthermore, loss of thyroid hormones may lead to low free thyroid hormone levels unless production is increased under the influence of thyroid stimulating hormone (TSH).[81,82] Four studies including 49 patients documented urinary loss of thyroid hormones and thyroxin-binding globulin (TBG) in patients with proteinuria.[83–86] In one study overt hypothyroidism was noted in two patients that resolved after remission of the nephrotic syndrome.[33] In a study of 159 patients with proteinuria TSH concentration was significantly higher compared to controls, and negatively correlated with serum albumin.[82] Although subclinical hypothyroidism was more frequent in the patients (11.3% vs. 1.8%), overt hypothyroidism was seen in only one patient. The relevance of subclinical hypothyroidism needs further evaluation; however, special attention is needed in pregnant women with a nephrotic syndrome.

Anemia is often observed in the nephrotic syndrome, and may be related to urinary loss of transferrin. Low serum transferrin levels can reduce serum iron concentrations and occasionally cause microcytic anemia.[87] Because transferrin transports iron to erythroid cells, severe hypotransferrinemia per se can also cause microcytic anemia in the absence of iron store depletion.[88] Supplementation of iron is often not effective. Indeed in a study in six nephrotic children treatment with oral or IV iron did not increase hemoglobin (Hb) levels.[89] Moreover, breakdown of reabsorbed transferrin can liberate iron in renal tubules, which could play a role in the nephrotoxic effects of proteinuria.[90] Thus supplemental iron may not be without risk and should not be undertaken without clear evidence of iron deficiency.

Urinary loss of erythropoietin (EPO) may also contribute to anemia in patients with a nephrotic syndrome. Erythropoietin is lost in the urine of nephrotic patients, but synthesis is not increased.[88] Administration of EPO has been successfully used in nephrotic patients, with normal renal function and repleted iron and vitamin B12 stores, resulting in a significant increase in hemoglobin levels.[89,91]

Serum levels of 25-hydroxyvitamin D, a precursor of active vitamin D (calcitriol), are reduced in the nephrotic syndrome because of urinary loss of vitamin D binding protein.[92,93] Low levels of free serum calcitriol have also been reported resulting in hypocalcemia (low ionized serum calcium or low total serum calcium corrected for albumin concentration).[94–96]

If left untreated, these metabolic disturbances can lead to secondary hyperparathyroidism and bone lesions, such

as osteomalacia and osteitis fibrosa.[96] Unfortunately, there are little data available to guide treatment. In patients with nephrotic syndrome and normal renal function, daily treatment with 1,000 IU vitamin D (cholecalciferol or ergocalciferol) seems reasonable if 25-hydroxyvitamin D deficiency causes low ionized or corrected total serum calcium levels. Depending on the response, higher doses may be necessary.

Thromboembolism

Patients with a nephrotic syndrome are at increased risk for venous and arterial thrombosis. Older studies reported an overall incidence of renal vein thrombosis of 2% to 42%, of venous thrombosis 8% to 42%, of pulmonary embolism 9% to 21%, and of arterial thrombosis 4%.[97–99] Sometimes the thrombotic event is the presenting event. The increased risk of thrombosis is attributed to variable urinary losses and hepatic production of anticoagulant and procoagulant factors. In patients with a nephrotic syndrome increased concentrations of fibrinogen, factor VIII, and plasminogen activator inhibitor-1, and decreased levels of antithrombin III, plasminogen, and free protein-S have been reported.[100] This imbalance of the coagulation cascade results in a prothrombotic state. The risk of thrombosis is dependent on serum albumin levels. Two studies reported serum albumin levels of 1.5 ± .3 and 2.2 ± .6 g per dL in patients with and 2.6 ± .5 and 2.8 ± .9 g per dL in patients without thrombosis.[101,102] The majority of patients with thrombosis had serum albumin levels below 2.5 g per dL. Risk of thrombosis not only depends on serum albumin level but also on the underlying glomerular disease. Sarasin showed a two- to threefold increased risk of thrombosis in patients with idiopathic membranous nephropathy.[103] This was confirmed in a study in children.[104] The question of prophylactic anticoagulation has not been answered by prospective randomized trials. Most authors agree that patients with a membranous nephropathy and a serum albumin levels below 2.0 g per dL are at highest risk and should be considered for prophylactic anticoagulant therapy. Obviously, anticoagulation is needed in patients with risk factors for venous thromboembolism (VTE), which include a history of VTE, prolonged immobilization, congestive heart failure, morbid obesity, and abdominal, orthopedic, or gynecologic surgery.[105]

A recent retrospective study reported a high incidence rate in the first 6 months after onset of the nephrotic syndrome.[97] The incidence rate was 9.85% for VTE and 5.52% for arterial thromboembolism (ATE), a risk 140 times and 50 times higher than in the general population. In this study, neither proteinuria nor serum albumin, but rather the ratio of proteinuria to serum albumin predicted VTE. Of note, neither proteinuria nor albumin were associated with ATE, in contrast to eGFR, and known cardiovascular risk factors. This study confirmed the high risk of pulmonary embolism (PE), which exceeded the risk of deep vein thrombosis (DVT; ratio 1.3:1), whereas in the normal population the ratio PE:DVT = 1:2. The high incidence of PE is attributed to the presence of silent renal vein thrombosis in the nephrotic syndrome. The incidence of VTE and ATE decreased to values of 1% per year during follow-up. It is unclear if this reflects the true natural history, or is the mere consequence of the treatment of the nephrotic syndrome with the associated improvement in proteinuria.

Infections

Patients with a nephrotic syndrome not only develop hypoalbuminemia, but frequently also have hypogammaglobulinemia. Patients with a nephrotic syndrome are at risk for infections, notably pneumonia and peritonitis caused by encapsulated bacteria such as Streptococcus and Haemophilus. Infections were the main cause of death in children with a nephrotic syndrome before the introduction of antibiotics and prednisone. One study reported that infections in patients with proteinuria were independently associated with low serum immunoglobulin G (IgG) levels (<600 mg per dL).[106] Administration of IgG resulted in a decreased rate of bacterial infections to a level equal to that in patients with endogenous levels over 600 mg per dL.

Cardiovascular Disease and Progressive Renal Failure

An abnormal lipid metabolism is almost always present in patients with nephrotic syndrome. Both increased hepatic production of lipoproteins and decreased lipid catabolism play a role. Most prominent are an increased low-density lipoprotein (LDL) cholesterol level, hypertriglyceridemia, and an increased lipoprotein (a) [Lp(a)] level.[107,108]

The increase in Lp(a) is explained by an increased rate of synthesis.[109] The increase in LDL cholesterol appears to be partly mediated by a reduced hepatic cholesterol uptake due to an acquired LDL-receptor deficiency.[110] Studies in experimental animals point to an inefficient translation and/or increased LDL-receptor turnover as a cause for LDL-receptor deficiency.[111,112] Intracellular free cholesterol is further reduced by an increase in liver-specific acylcoenzyme A:cholesterol acyltransferase-2 (ACAT-2), the enzyme responsible for esterification of cholesterol in hepatocytes.[112,113] The reduction in hepatocellular free cholesterol can lead to upregulation of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate limiting enzyme involved in synthesis of cholesterol.[114] These mechanisms all lead to increased LDL cholesterol levels. Despite the severe hypercholesterolemia in nephrotic syndrome, cholesterol 7-hydroxylase, which is the rate-limiting step in cholesterol conversion to bile acid, remains unchanged.[115]

Hypertriglyceridemia is the consequence of the inability to clear triglyceride-rich lipoproteins (VLDL, chylomicrons, and remnant particles). Several factors contribute to reduced clearance of lipoproteins in the nephrotic syndrome. Hypoalbuminemia leads to reduced amounts of endothelial bound lipoprotein lipase (LPL), resulting in decreased clearance of lipoproteins.[116] However this defect only leads to a mild increase in triglycerides.[117] More important is a

deficiency in apolipoprotein (apo) E content of lipoproteins that decreases their ability to bind to LPL.[118] Shearer et al. demonstrated that binding of VLDL from nephrotic rats to endothelial cells is markedly reduced compared to controls, whereas binding of VLDL from rats with hereditary analbuminemia is increased compared to controls.[119] They also noted that HDL of nephrotic rats was deficient in apo E compared to analbuminemic and control rats. Since lipoproteins acquire apo E from HDL, the decreased clearance of lipoproteins may be caused by a reduced apo E content of nephrotic HDL.[110] Indeed, the defective binding of nephrotic VLDL was reversed by preincubation of nephrotic VLDL with HDL from either normal or analbuminemic rats but not by preincubation with nephrotic HDL.[119]

The combination of increased LDL-cholesterol, triglycerides, and Lp(a) is highly atherogenic and carries a five- to sixfold increased risk for myocardial infarction and a two- to threefold increased risk of coronary death compared to age- and sex-matched controls.[120] Lipid-lowering treatment, preferably with HMG-CoA reductase inhibitors, is indicated if proteinuria is expected to persist for at least several months or renal insufficiency is present.[121,122] In addition, reduction in protein excretion with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) results in a significant decline in LDL cholesterol and lipoprotein(a).[123] Although dietary restriction of cholesterol and saturated fat is advised, it is generally of limited value.

Proteinuria is an important risk factor and the best predictor of progression to ESRD in nephrotic syndrome.[124,125] Reducing proteinuria can prevent progression to renal failure and improve complications associated with nephrotic syndrome, such as hypoalbuminemia, hyperlipidemia, and edema. Strict blood pressure control is the most important measure to reduce proteinuria.[124] ACE inhibitors or, in case of side effects, ARBs are the preferred agents, as they reduce proteinuria and slow progression of kidney disease more effectively than other antihypertensive agents.[126–128] ACE inhibitors and ARBs act by reducing the intraglomerular pressure and by improving the size-selective properties of the glomerular capillary wall, both of which contribute to reducing protein excretion. ACE inhibitors and ARBs should not be started at the same time as the loop diuretic, because the combined effects of intravascular volume depletion and impairment of autoregulation increase the risk of acute renal failure. Low-dose ACE inhibitors and ARBs can be introduced once a stable dose of the loop diuretic is reached and slowly titrated upwards. Target blood pressures are $\leq$125/75 mm Hg in patients with proteinuria $\geq$1 g per day and $\leq$130/80 mm Hg if proteinuria falls below $<$1 g per day.[129] Proteinuria should be reduced to 0.5 g per day, although this target often is difficult to reach in patients with nephrotic syndrome.[130]

Dietary Protein

A high dietary protein intake should be avoided in patients with nephrotic syndrome because this can increase the rate of protein catabolism and urine protein excretion.[131] In contrast, protein restriction has been shown to slow renal function deterioration in patients with diabetic and nondiabetic renal diseases.[132] However, the optimal level of protein intake is unclear, and care must be taken to avoid malnutrition. Therefore, in patients with nephrotic syndrome a moderate protein restriction of 0.8 to 1 g per kg body weight per day plus urinary protein loss is advised while maintaining a normal caloric intake (35 kcal per kg per day).[133]

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